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ORIGINAL RESEARCH

High Use of SABAs is Associated with Higher Exacerbation Rate in Dutch Patients with Asthma

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Purpose: Many patients with asthma still have insufficient disease control, despite the availability of effective treatment options. A substantial proportion of patients appear to rely more on short-acting beta$_2$-agonist (SABA) rather than on anti-inflammatory maintenance treatment. The aim of this study was to describe differences in indicators of asthma symptoms and exacerbations among patients using more or less SABA than the guideline-recommended threshold of <3 times/week.

Patients and Methods: Data from Dutch respondents in the European REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey were used in this post hoc analysis. The survey included asthma patients aged 18–50 years with at least two prescriptions for their asthma in the past two years. SABA use was categorized into two groups: <3 (low-SABA users) or ≥3 (high-SABA users) times in the last week.

Results: Of the 736 asthma patients, 21% did not use SABA and 19% used SABA 1 to 2 times (all low SABA users) and 60% used SABA ≥3 times (high SABA users) in the last week. The majority of high and low SABA users also reported using an ICS-containing treatment. Significant differences were found for all indicators related to exacerbations ($p<0.001$): high SABA users more frequently used antibiotics and oral steroids, more frequently visited the emergency departments or needed an overnight hospital stay. Indicators of asthma symptoms were not significantly different between both groups.

Conclusion: The majority of a Dutch asthmatic population reported high SABA use and had frequent moderate/severe exacerbations. More effective interventions are needed to change healthcare providers' and patients' behaviours to improve care and reduce SABA (over)use.

Keywords: asthma, short acting beta2-agonist, SABA, primary health care, adverse effects, guidelines

Introduction

According to the Global Initiative for Asthma (GINA) report in 2019, the primary goals of asthma management are to achieve and enhance control of disease, minimize future risk of exacerbations/deaths and reduce fixed airflow limitation, while at the same time minimizing side effects of treatment. In clinical practice, meeting these goals and thus managing uncontrolled asthma involves a continuous cycle of regular patient assessment, review of medications, treatment adjustment, and evaluation of the patient's response to facilitate treatment decisions.[1]

Despite the guidelines and the availability of multiple effective treatment options, asthma control is still inadequate in many patients. In Europe, a large proportion of asthma patients has uncontrolled asthma.[2] A web-survey in over 2500

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Australian adults with asthma revealed poor self-rated symptom control in approximately half of the participants, with one-third of patients reporting an urgent healthcare need in the previous year.[3] Poor asthma control is strongly associated with a higher risk of exacerbations, poor quality of life, reduced productivity and increased healthcare utilization.[4,5]

A marker for poor asthma control is high use of short-acting beta$_2$-agonists (SABA).[6] Many patients appear to rely primarily on their SABA rather than their anti-inflammatory controller therapy (inhaled corticosteroids (ICS)), thereby failing to treat the underlying inflammation resulting in uncontrolled asthma.[6,7] Moreover, high use of SABA therapy comes with a range of adverse consequences, including increased asthma-related mortality and asthma-related healthcare utilization.[8–10] In addition, the dispensation of more than twelve SABA inhalers to one individual per year is associated with an increased risk of asthma-related mortality.[11]

One of the aspects that may encourage high SABA use is the fundamental asthma management principle of using SABA exclusively on an "as needed" basis.[12] This has been the main recommendation for many years, causing SABA use to become habitual under asthma patients. GINA has recognised this unfortunate by-effect and has therefore decided to make a drastic change in their updated report regarding the recommendations on SABA use in asthma management. In GINA's 2019 report, it is highlighted that for the safety of the patients, SABA-only treatment is no longer recommended for asthma treatment in adults and adolescents not even in the milder stages of asthma. As a replacement, the combination of an as needed ICS with a fast-acting long-acting beta$_2$-agonist (LABA) is now recommended as the initial starting treatment for patients with mild asthma. This strategy is beneficial to the exacerbation rate as well as to symptoms.[1]

The Dutch general practitioners' (GPs') asthma guidelines define high SABA use as the use of 3 or more SABAs per week. In the case of high SABA use, patients should consult the GP for evaluation of the medication strategy. The use of 3 or more SABAs per week is regarded as a cut-off for adding ICS and 2 times or less needs no additional therapeutic adjustments. This places the Dutch GP guidelines in accordance with the GINA 2018 recommendation.[13–15] For healthcare providers to achieve an optimal informed clinical decision making and an easy assessment of SABA, more insight is needed into the (high) SABA use in the previous week as reported by the patient. The current study reviews SABA usage in the Netherlands and studies whether there are differences in indicators of asthma symptoms and exacerbations between patients using either more or less SABA than the threshold of 3 times/week.

Patients and Methods

Study Design and Population

This descriptive study is based on a post hoc analysis on data of Dutch respondents to the European REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey.[2,16]

The REALISE survey was conducted online in eleven European countries (Austria, Belgium, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) in 2012, by Incite Marketing Planning Limited (London, United Kingdom), in accordance with the Codes of Conduct of the Market Research Society, European Pharmaceutical Marketing Research Association and Association of the British Pharmaceutical Industry, and guidelines from the British Healthcare Business Intelligence Association. Data were managed in accordance with the Data Protection Act (UK, 1998). It was a qualitative, online questionnaire-based survey that included asthma patients aged 18–50 years with at least two prescriptions for asthma treatment in the past two years. In the Netherlands, 855 respondents completed the REALISE survey. Patients with COPD as a comorbidity were excluded from the main study analysis. Patients with asthma and concomitant COPD were analyzed separately. In accordance with Dutch regulations, ethical approval and additional written informed consent was not required for this post hoc analysis, as all study data were anonymised.

Tools and Indicators

The REALISE questionnaire was developed by the core study members (fully listed in the acknowledgements) and required approximately 30 minutes for completion. The survey made use of validated consumer panels. These panels met the International Organization for Standardization (ISO:20,252) quality standards. Multiple panels were used to reduce potential bias. Detailed information on the REALISE study design, population, sample size, tools, and processes are reported in the REALISE study's protocol.[2]

SABA use was categorized into two groups of patients either using more of less SABA than the recommended threshold: <3 (low SABA users) or ≥3 (high SABA users) times in the last week. Indicators of asthma symptoms included the number of days with symptoms, normal activities affected by symptoms, and awakening at night, all during the 7 days preceding the survey. Indicators of exacerbations over the last 12 months included the number of antibiotics and oral steroid courses needed due to the worsening of asthma symptoms (defined as moderate exacerbations), the number of emergency department visits and overnight hospital stays due to asthma (defined as severe exacerbations).

Statistical Analysis

Statistical analysis was performed using IBM SPSS (version 25) and all tests were two-tailed at a 0.05 level of significance. Differences in indicators of asthma symptoms and exacerbations were assessed using the chi-square test or Fisher's exact test for the dichotomous variables and the Mann–Whitney *U*-test for non-normally distributed continuous variables. Descriptive statistics were used to describe the respondent's demographics and characteristics.

Binary logistic regression modelling was used to investigate the relation between SABA use (below or above the threshold recommended in guidelines) and moderate and severe exacerbations. Adjustments were made for the following potential confounders: age, gender and ICS-containing treatment. Additional confounders (comorbidities, smoking status and number of years since asthma diagnosis) were added based on their univariate relation ($p<0.20$) with the dependent or independent variable if the maximum number of parameters for a model, set at 10% of the lowest number of events, was not exceeded. Comorbidities (COPD, diabetes, depression, heart disease, high blood pressure, rheumatoid arthritis and cancer) were combined into a combination score, based on the Charlson Comorbidity Index's scoring system.[17] Our combined comorbidity score ranges from 0 to 8; one point for each comorbidity with the exception of cancer, which counts for two points.

Results

Frequency of SABA Use

Of the 855 Dutch participants who completed the REALISE survey, 817 patients with asthma answered the question regarding SABA use ("Thinking about the last week. How many times have you used your reliever inhaler? (This is usually a blue colour)"). Of these 817 respondents, 81 had a co-diagnosis of COPD. The final study population, therefore, consists of 736 respondents with asthma. Of the 736 respondents, 73.4% (n=540) were female, and the median age was 36 years.

Of the 736 respondents, 60.1% (n=442) used SABA ≥3 times in the last week. An additional 18.6% (n=137) used SABA 1 or 2 times and 21.3% (n=157) did not use any SABA in the last week (Figure 1).

The largest group of high SABA users (42.8%) was 41–50 years old, while this was 26–40 years for low SABA users (42.5%). Further variations were observed in co-morbidities and treatment type. High SABA users were significantly more frequently treated with a combination inhaler (ICS/LABA) or oral treatment (the type of oral treatment was not specified) in comparison to low SABA users, respectively, 34.4% vs 25.2%, p=0.009; 20.1% vs 6.5% $p<0.001$ (Table 1).

Differences in Patient Outcomes Based on SABA Use

A total of 58.4% (n=258) of the high SABA users, and 42.9% (n=126) of the low SABA users reported using an antibiotic course for an asthma-associated condition more than once in the last 12 months ($p<0.001$) ("How many times in the past year have you needed a course of antibiotics because you experienced other health problems related to your asthma, e.g. chest infections/bronchitis/stubborn cough etc?"). (Figure 2)

Similarly, 45.5% (n=201) of the high SABA users and 21.8% (n=64) of the low SABA users, reported using an oral steroid course for worsening of asthma more than once in the last 12 months ($p<0.001$) ("How many times have you needed a course of steroid tablets for worsening asthma? (In the last 12 months …)"). In total 14.9% (n=66) of the high SABA users and 3.4% (n=10) of the low SABA users had one or more emergency department visit due to asthma in the last 12 months ($p<0.001$) ("How many times have you been treated in Accident and Emergency or the hospital emergency department for your asthma in the past 12 months?"). Finally, 8.4% (n=37) of the high SABA users and 1.4% (n=4) of the low SABA users had one or more overnight hospital stay due to asthma in the last 12 months ($p<0.001$) ("How many times have you been hospitalised and had to stay

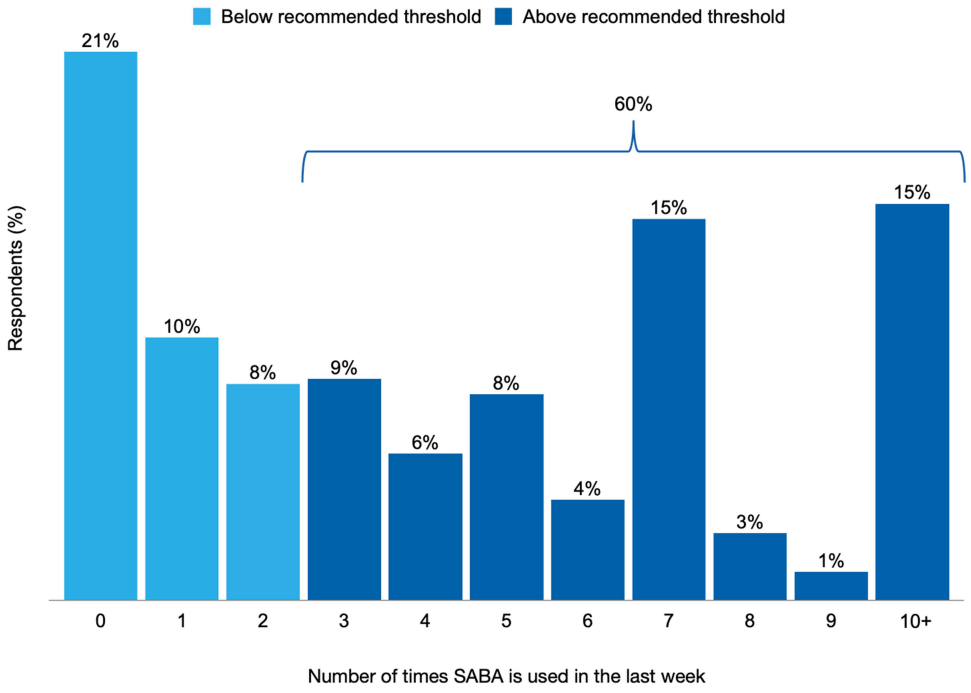

Figure 1 SABA usage in the last week (n=736).
Notes: Survey question: "Thinking about the last week. How many times have you used your reliever inhaler? (This is usually a blue colour)"; The reported percentages are rounded to whole numbers.

overnight in a hospital as a result of your asthma in the past 12 months?") (Figure 2).

No significant differences were found between the two SABA groups when testing for the indicators of asthma symptoms. A slight majority, 55.0% (n=243) of the high SABA users and 56.5% (n=166) of the low SABA users reported that their normal activities were not affected by symptoms ("How many days has asthma interfered with your normal activities (eg sport, school, work/housework)? (Thinking about the last 7 days …)") (Figure 3A) and 48.9% (n=216) of the high SABA users and 50.3% (n=148) of the low SABA users did not have any nighttime awakenings due to asthma symptoms ("How many nights have you been affected/woken up by asthma symptoms (including cough)? (Thinking about the last 7 days …)") (Figure 3B). Nevertheless, 81.4% (n=360) of the high SABA users and 78.6% (n=231) of the low SABA users reported 1 or more days with asthma-related symptoms ("How many days have you experienced asthma symptoms? (Thinking about the last 7 days …)") (Figure 3C).

A multiple logistic regression analysis revealed that high SABA users more frequently experienced moderate and severe exacerbations independently of confounders (OR 1.8 (95% CI 1.3–2.5) and OR 4.4 (95% CI 2.3–8.7), respectively) (Table 2). The logistic regression models of the other exacerbation variables are shown in the Supplementary Table S1.

Controller Use

A total of 68.3% (n=142) of the high SABA users who reported having been prescribed a controller inhaler (n=208), indicated in the survey that they use this inhaler every day. In contrast, less than half (49.6% (n=59)) of the low SABA users on controller therapy (n=119), indicated using their controller inhaler every day ("Which statement best describes how you take your regular asthma treatment. This is your preventer inhaler, which is usually brown, orange or red.").

Asthma and Concomitant COPD

Similar analyses were also performed for all 817 patients who completed the question regarding SABA use, including on data from the 81 asthma patients with co-existing COPD. These results are presented in Supplementary Table S2 and Supplementary Figures S1–S3. In this subgroup of 81 asthma patients with co-existing COPD, 77.8% (n=63) used SABA ≥ 3 times in the last week. Furthermore, 14.8% (n=12) reported using SABA 1 or 2 times and 7.4% (n=6) did not use any

Table 1 Demographics and Characteristics as Reported by Respondents According to SABA Use (n=736)

	Respondents with <3 SABA (Low-SABA Users) in the Last Week 39.9% (n=294)	**Respondents with ≥3 SABA (High-SABA Users) in the Last Week 60.1% (n=442)**	**P values[a]**
Gender, % (n)			
Female	75.2% (n=221)	72.2% (n=319)	P=0.395
Male	24.8% (n=73)	27.8% (n=123)	
Age, years, median [IQR]	34 [25–42]	38 [29–45]	**P<0.001**
Age range, years, % (n)			
18–25	25.5% (n=75)	17.0% (n=75)	**P=0.003**
26–40	42.5% (n=125)	40.3% (n=178)	
41–50	32.0% (n=94)	42.8% (n=189)	
Year since asthma diagnosis, % (n)			
Data available	83.3% (n=245)	88.5% (n=391)	
1 or less	5.7% (n=14)	7.2%(n=28)	P=0.478
2–5	12.7% (n=31)	10.5% (n=41)	
6–10	15.9% (n=39)	12.8% (n=50)	
11 or more	65.7% (n=161)	69.6% (n=272)	
Current smokers, % (n)	25.9% (n=76)	24.0% (n=106)	P=0.601
Co-morbidities*, % (n)			
Diabetes	3.1% (n=9)	7.0% (n=31)	**P=0.020**
Depression	14.6% (n=43)	15.4% (n=68)	P=0.834
Heart disease	1.4% (n=4)	2.3% (n=10)	P=0.425
High blood pressure	7.5% (n=22)	14.0% (n=62)	**P=0.006**
Rheumatoid arthritis	4.1% (n=12)	8.6% (n=38)	**P=0.017**
Cancer	0.7% (n=2)	1.4% (n=6)	P=0.487
Comorbidity Index			
0	74.8% (n=220)	63.8% (n=282)	**P=0.002**
1	20.7% (n=61)	24.9% (n=110)	
2	2.7% (n=8)	9.3% (n=41)	
3	1.0% (n=3)	1.6% (n=7)	
4	0.7% (n=2)	0.5% (n=2)	
5	0.0% (n=0)	0.0% (n=0)	
6	0.0% (n=0)	0.0% (n=0)	
7	0.0% (n=0)	0.0% (n=0)	
8	0.0% (n=0)	0.0% (n=0)	
Treatment type[#], % (n)			
Reliever (SABA)	75.9% (n=223)	73.5%(n=325)	P=0.723
Preventer (ICS)	40.5% (n=119)	47.1% (n=208)	P=0.082
Combination inhaler (ICS/LABA)	25.2% (n=74)	34.4%(n=152)	**P=0.009**
Oral treatment	6.5% (n=19)	20.1% (n=89)	**P<0.001**
Other asthma medication	5.4% (n=16)	14.5% (n=64)	**P<0.001**

Notes: *Self-reported as having been diagnosed by a doctor; [a]p values are two sided for the difference between <3 SABA and ≥3 SABA groups (significant differences are marked bold); [#]Which of the following treatments do you currently take to help manage your asthma? - multiple answers possible.

Abbreviations: SABA, short-acting beta2 agonist; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long acting beta2 agonist.

SABA in the preceding week (Supplementary Figure S4). Of these 81 asthma patients with COPD, the high SABA users more frequently visited the emergency department and had one or more overnight hospital stays in the last 12 months than the low SABA users (Supplementary Figure S5). There were no significant differences between both SABA groups with regard to asthma symptoms (Supplementary Figure S6).

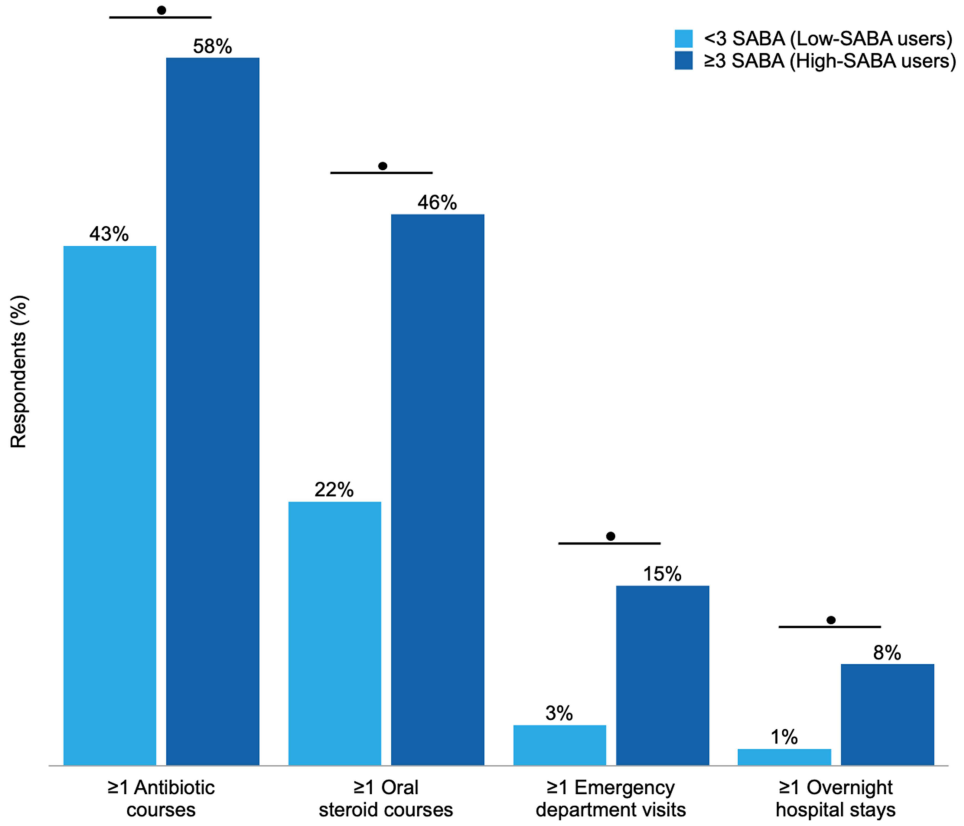

Figure 2 Indicators of exacerbations (n=736), according to SABA use (<3 times or ≥3 times/week).
Notes: <3 SABA (Low-SABA users) n=294; ≥ 3 SABA (High-SABA users) n=442; P values are two sided; The reported percentages are rounded to whole numbers. •Significant difference p<0.001.

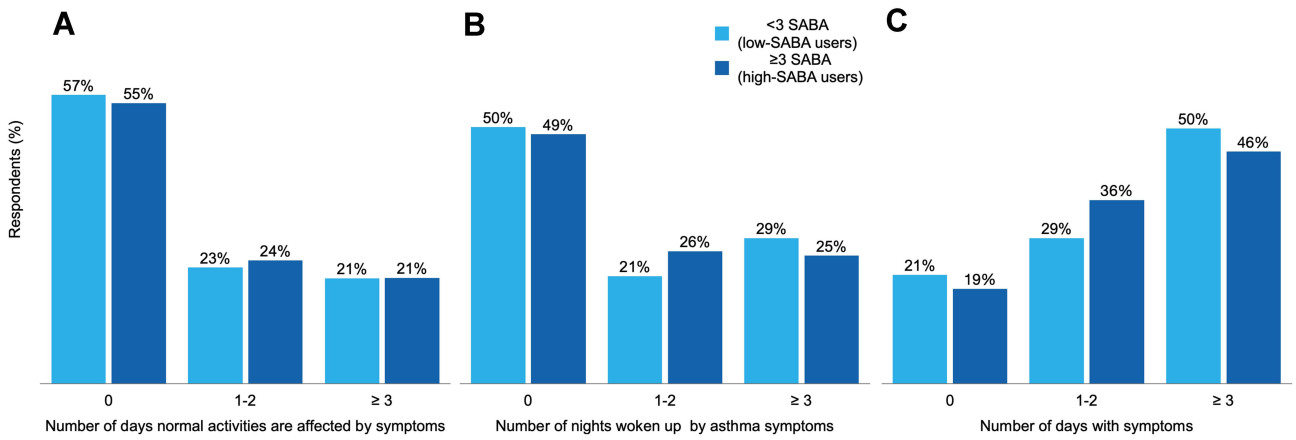

Figure 3 Indicators of asthma symptoms (n=736), according to SABA use (<3 or ≥3 times/week).
Notes: <3 SABA (Low-SABA users) n=294; ≥3 SABA (High-SABA users) n=442; P values are two sided, (**A**) p=0.895, (**B**) p=0.265, (**C**) p= 0.109; The reported percentages are rounded to whole numbers.

Discussion

This analysis of the Dutch asthmatic population from the REALISE study revealed substantial high SABA use: 60% of the asthma patients used SABA above the guideline-recommended threshold for ICS addition or other step-up treatment (<3 times/week). High SABA users (≥3 times/week) experienced more moderate or severe exacerbations even after the statistical model was adjusted for

Table 2 Relation Between Moderate (A)/Severe (B) Exacerbations and SABA Use Adjusted for Confounders (n=736)

Predictors	Coefficients (SE)	p-value	OR	95% CI for OR	
				Lower	Upper
A: Relation between moderate exacerbations and SABA use adjusted for confounders					
SABA use (0= low SABA users; 1= high SABA user)	0.600 (0.160)	P<0.001	1.822	1.332	2.491
Age	−0.002 (0.008)	0.777	0.998	0.981	1.014
Gender (0= male; 1= female)	−0.511 (0.184)	0.005	0.600	0.418	0.860
Using ICS containing treatment (0= not using ICS; 1= using ICS)	0.037 (0.176)	0.833	1.038	0.735	1.466
Smoking status (0= no smoker; 1= smoker)	0.234 (0.182)	0.200	1.264	0.884	1.807
Comorbidity Index	0.432 (0.123)	P<0.001	1.541	1.211	1.961
B: Relation between severe exacerbations and SABA use adjusted for confounders					
SABA use (0= low SABA users; 1= high SABA user)	1.485 (0.342)	P<0.001	4.417	2.260	8.663
Gender (0= male; 1= female)	−1.291 (0.262)	P<0.001	0.275	0.165	0.460
Using ICS containing treatment (0= not using ICS; 1= using ICS)	−0.041 (0.280)	0.885	0.960	0.554	1.664
Comorbidity Index	0.582 (0.141)	P<0.001	1.789	1.357	2.360

Notes: The confounders comorbidities, smoking status and number of years since asthma diagnosis were added to the models based on their relation (p<0.20) with the dependent or independent variable. The variable age was not added to model B since the linearity assumption was not met.
Abbreviations: SABA, Short-acting Beta-agonist; SE, standard error; OR, Odds ratio; CI, Confidence interval; ICS, Inhaled corticosteroids.

confounders. Nevertheless, no differences in symptoms were observed between low SABA users and high SABA users; this might, among other explanations, be due to the beneficial effect of SABA on symptom reduction.

High SABA Use

The unexpectedly large proportion of high SABA users calls for an explanation. It is known that survey participants tend to give socially desirable answers,[18] which, if this was the case, would imply that the actual proportion of high SABA users maybe even higher. One of the more recent studies investigating SABA use is the Australian survey of Azzi et al.[6] This paper reported an even higher percentage of high SABA users (70.1%) than our study. However, the situation in Australia is not quite comparable to the Netherlands, as in Australia, SABA are sold over the counter, ie without a doctor's prescription.

Association of High SABA Use with Exacerbations

Our findings that high SABA users experienced more moderate and severe asthma exacerbations and also more often had a history of courses of antibiotics and oral steroids, are in line with findings in other studies.[6,8,19–24] This could imply that SABA usage in the preceding week can be extrapolated to SABA use in the previous year. Hence, this shows that a clinically easy and quick way of assessing SABA use, ie by merely asking the patient about their SABA use in the preceding week, could be an indicator for the risk of future exacerbations.

Association of High SABA Use with Symptoms

In our study, there were no signs of significant variations between SABA groups with regard to symptoms. Nevertheless, other studies have stressed the association of SABA overuse with asthma-related symptoms and quality of life.[6,25] The different outcomes between studies may be explained by the differences in methods and investigated symptoms. However, the high SABA users in our study may have rated their symptoms as less frequent since they use their SABA solely to minimize their symptoms. In line with this, it is conceivable that high SABA users would experience more symptoms when they use their SABA less frequently or not at all. Furthermore, it has been reported that patients underreport their symptoms because of a lack of accurate perception of their actual asthma control. In such cases, patients tolerate their symptoms because they perceive them to be their "standard".[26] The possibility that the participants in the current survey also underreported their symptoms cannot be ruled out.

It seems remarkable and somewhat contradictory that approximately 50% of the patients reported that their normal activities are not affected by symptoms, whereas only 20% of

the patients claimed not to have any symptoms at all. Moreover, almost half of the patients in our study reported that their daily activities were affected or that they had nighttime awakening due to asthma symptoms, and over 45% of the patients in our study reported that they experienced asthma symptoms 3 or more days per week. These symptoms often lead to a higher burden of disease, negatively impacting quality of life, or leading to depression, higher asthma-related costs and an increased overall risk of exacerbations.[6,8,20]

SABA Use in Patients with Asthma and COPD

Also, patients with both asthma and COPD used their SABA inhaler more frequently than the guideline-recommended threshold (<3 times/week). The proportion of high SABA users in these patients was even higher than in the group of patients with only asthma. However, as-needed SABA is part of the standard treatment for patients with COPD.[27] Patients with both asthma and COPD experience more symptoms and exacerbations than patients with COPD or asthma.[28] Therefore, these patients may more frequently need their SABA inhaler for symptom reduction. However, there is a limitation to our findings regarding this subgroup, as the studied population sample is quite small. Therefore, further research into SABA use in patients with both asthma and COPD is required.

ICS Underuse

Adherence to ICS is estimated to range between 25% and 80%.[29–31] It is also known that the adherence to ICS varies over time, improving towards and immediately after an asthma exacerbation. Poor compliance or absent adherence to ICS are strongly associated with more frequent exacerbations.[28] This is the reason why improvement of adherence to ICS is a cornerstone element in the treatment strategy of asthma control.

Our study showed that more high SABA users reported using their controller inhaler on a daily basis (68%) than low SABA users (50%). A possible explanation for this finding is that high SABA users in this study potentially had more asthma symptoms than low SABA users, therefore increasing both ICS and SABA usage in conjunction with one another. This makes sense as high SABA use is associated with more severe disease, which in its turn warrants more reliever use. This certainly does not apply to the patients with high SABA use who are not using an ICS all together. A change in prescribing behavior, ie no longer prescribing SABA on an as needed basis, but initiating treatment by prescribing an ICS/LABA as recommended in the GINA 2019 guidelines, may prove to be of vital impact in the reduction of high SABA use among asthma patients.[1] Starting treatment with an ICS/LABA may help patients to improve their ICS adherence, thereby simultaneously treating the underlying disease instead of using their SABA as a quick solution to reduce their symptoms.

Future Challenges

Future research should focus on assessing patients' habits, behaviors and opinions (next to prescribers') towards the (appropriate) use of SABA.[32] In addition, it is important to focus on approaches for informing and training asthma patients with regard to their symptoms and asthma control. The type of SABA inhaler also deserves prompt attention both in terms of future research goals and GPs' daily prescription practices.[21] Overall, questions remaining to be addressed are how asthma care could be improved, received and adopted and how appropriate use of SABA could be comprehended and managed by the GP, but also by other healthcare professionals and the patient.[16]

Strengths and Limitations

The findings of the current study convey new insights on high SABA use and differences in symptoms and exacerbations in a Dutch asthmatic population. Although the nature of the study design, which is an online survey, may have inserted some limitations, our findings could support future research hypotheses and highlight several challenges.

The core limitation is information-bias and recall-bias due to the fact that all data were self-reported and could not be clinically verified. Therefore, inaccurate responses due to poor recall cannot be excluded. Furthermore, the fact that this population was not derived from the general Dutch population but from consumer panels and included only those aged 18–50 years using social media, may restrict the generalizability of the findings. However, it is believed that it will not have a significant effect on the study conclusions since the majority of the wider Dutch population is familiar with social media. Nonetheless, it cannot be excluded that the people signing up for the consumer panels may have different characteristics than those who do not sign up, and may therefore, have biased our results.

Unfortunately, asthma severity and medication, specifically adherence, was only a small aspect of the REALISE survey. Therefore, no information regarding the asthma severity of the patients was available, nor detailed information regarding the usage of ICS, including the duration of the treatment and adherence. Because of this, no thorough examination of the asthma severity and ICS adherence for the high SABA users and the low SABA users could be performed.

Unfortunately, there was no information available regarding patients' reasons for high use of SABA. However, previous research has established several reasons for SABA overuse; 1) patients are not aware that high SABA use is an indicator for poor asthma control, 2) patients feel an emotional attachment to their SABA reliever, due to its ability to quickly relieve symptoms, and 3) patients do not understand the necessity for ICS usage, especially when they do not experience symptoms. On a side note, it has been observed that severe exacerbations temporarily improve adherence to ICS.[33]

Furthermore, it is important to note that in our study use of SABA in de preceding week is associated with exacerbations in the last 12 months. Our results could therefore be biased by reverse causality. Nevertheless, the relationship between SABA use and exacerbation rate was also demonstrated in studies measuring SABA overuse based on the number of canisters used in the last year.[24] This could imply that SABA usage in the preceding week can be extrapolated to SABA use in the last year. This would make for a clinically easily accessible and quick way to assess SABA use, and apply this as an indicator for future exacerbation risk.

Taking into consideration the aforementioned limitations, the study still offers valuable insights in the use of SABA, specifically for the Dutch asthmatic population. In addition, many of these findings seem directly relevant as well to other European countries with similar asthma care.

Conclusions

Asthma control in the Netherlands remains poor, in line with the pattern observed in other European countries.[2] This poor control is associated with high use of SABA. Although tools and clinical guidelines are widely available, there is still a marked gap between guidelines and daily practice. Symptoms and exacerbations are common in this Dutch asthmatic population, while exacerbations tend to vary significantly between low SABA users and high SABA users. Such symptoms and exacerbations may result in a strong adverse impact on patients' quality of life, hospitalizations and asthma-related deaths. Both healthcare providers and patients should interpret high SABA use more diligently as a marker of poor asthma control. To change their behaviours, more effective interventions are needed to improve asthma care and reduce SABA (over)use.

Data Sharing Statement

The data analyzed in this study belong to the original authors of the REALISE survey. They can be contacted about the availability of the data.

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Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2019. Available from: www.ginasthma.org. Accessed June 23, 2021.
2. Price D, Fletcher M, van der Molen T. Asthma control and management in 8000 European patients: the REcognise Asthma and Link to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med*. 2014;24:14009.
3. Reddel HK, Sawyer SM, Everett PW, Flood PV, Peters MJ. Asthma control in Australia: a cross-sectional web-based survey in a nationally representative population. *Med J Aust*. 2015;202(9):492–496. doi:10.5694/mja14.01564
4. Sims EJ, Price D, Haughney J, Ryan D, Thomas M. Current control and future risk in asthma management. *Allergy Asthma Immunol Res*. 2011;3(4):217–225. doi:10.4168/aair.2011.3.4.217
5. Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med*. 2011;105(6):930–938. doi:10.1016/j.rmed.2011.01.005
6. Azzi EA, Kritikos V, Peters MJ, et al. Understanding reliever overuse in patients purchasing over-the-counter short-acting beta2 agonists: an Australian community pharmacy-based survey. *BMJ Open*. 2019;9(8):e028995. doi:10.1136/bmjopen-2019-028995
7. Slejko JF, Ghushchyan VH, Sucher B, et al. Asthma control in the United States, 2008–2010: indicators of poor asthma control. *J Allergy Clin Immunol*. 2014;133(6):1579–1587. doi:10.1016/j.jaci.2013.10.028
8. Paris J, Peterson EL, Wells K, et al. Relationship between recent short-acting β-agonist use and subsequent asthma exacerbations. *Ann Allergy Asthma Immunol*. 2008;101(5):482–487. doi:10.1016/S1081-1206(10)60286-4
9. Sears MR. Deleterious effects of inhaled β-agonists: short-acting and long-acting agents differ. *Chest*. 2001;119(5):1297–1299. doi:10.1378/chest.119.5.1297
10. Anis AH, Lynd LD, Wang XH, et al. Double trouble: impact of inappropriate use of asthma medication on the use of health care resources. *CMAJ*. 2001;164(5):625–631.
11. Physicians, R.C.o. *Why Asthma Still Kills: The National Review of Asthma Deaths (NRAD) Confidential Enquiry Report*. London: RCP; 2014. Available from https://www.rcplondon.ac.uk/file/868/download. Accessed September, 2019.
12. Gibson P, Henry D, Francis L, et al. Association between availability of non-prescription beta 2 agonist inhalers and undertreatment of asthma. *BMJ*. 1993;306(6891):1514–1518. doi:10.1136/bmj.306.6891.1514
13. The IPCRG. Asthma guidelines used by primary care in Netherlands. Available from https://www.theipcrg.org/display/ResMapping/Netherlands%3A+Asthma. Accessed September 18, 2019.
14. NHG-Standaard Astma bij volwassenen (Derde herziening) Smeele I, Barnhoorn MJM, Broekhuizen BDL, Chavannes NH, et al. NHG-werkgroep astma bij volwassenen en COPD. NHG-standaard astma bij volwassenen (derde herziening)].
15. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2018. Available from: www.ginasthma.org. Accessed June 23, 2021.
16. van der Molen T, Fletcher M, Price D. Identifying patient attitudinal clusters associated with asthma control: the European REALISE survey. *J Allergy Clin Immunol Pract*. 2018;6(3):962–971. doi:10.1016/j.jaip.2017.10.007
17. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol*. 2008;61(12):1234–1240. doi:10.1016/j.jclinepi.2008.01.006
18. Turner C, Martin E, Eds. *Surveying Subjective Phenomena*. Vol 2. Russell Sage Foundation; 1984. Available from: www.jstor.org/stable/10.7758/9781610447003. Accessed January 10, 2020.
19. Yang JF, Chaudhuri R, Thomson NC, et al. Insights into frequent asthma exacerbations from a primary care perspective and the implications of UK National review of asthma deaths recommendations. *NPJ Prim Care Respir Med*. 2018;28(1):35. doi:10.1038/s41533-018-0103-9
20. Radzik D, Peroni DG, Pescollderungg L, Piacentini GL, Chatzimichail A, Boner AL. Nebulizers or pressurized metered-dose inhalers in the treatment of asthma exacerbations. *Allergy Asthma Proc*. 2005;26(3:207–209.
21. Johnston SL, Edwards MR. Mechanisms of adverse effects of β-agonists in asthma. *Thorax*. 2009;64(9):739–741. doi:10.1136/thx.2009.119230

22. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J*. 2020;55(4):1901872. doi:10.1183/13993003.01872-2019
23. Vervloet M, Weesie Y, Kocks JWH, Dijk L, Korevaar van J. *Asthma Medication in Dutch Primary Care. Asthma Medication Use and Its Relation with Asthma Outcomes*. Utrecht: Nivel; 2020.
24. Bloom CI, Cabrera C, Arnetorp S, et al. Asthma-related health outcomes associated with short-acting β_2-agonist inhaler use: an observational UK Study as part of the SABINA global program. *Adv Ther*. 2020;37(10):4190–4208. doi:10.1007/s12325-020-01444-5
25. Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 asthma insight and management survey. *Allergy Asthma Proc*. 2012;33(1):54–64. doi:10.2500/aap.2011.32.3518
26. Bosnic-Anticevich S, Kritikos V, Carter V, et al. Lack of asthma and rhinitis control in general practitioner-managed patients prescribed fixed-dose combination.
27. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2019.
28. Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol*. 2011;128(6):1185–1191. doi:10.1016/j.jaci.2011.09.011
29. Poulos LM, Cooper SJ, Ampon R, Reddel HK, Marks GB; Australian Institute of Health and Welfare. *Mortality from Asthma and COPD in Australia. Cat. No. ACM 30*. Canberra: AIHW; 2014.
30. Ponieman D, Wisnivesky JP, Leventhal H, Musumeci-Szabó TJ, Halm EA. Impact of positive and negative beliefs about inhaled corticosteroids on adherence in inner-city asthmatic patients. *Ann Allergy Asthma Immunol*. 2009;103(1):38–42. doi:10.1016/S1081-1206(10)60141-X
31. McKibben S, Bush A, Thomas M, Griffiths C. "Tossing a coin:" defining the excessive use of short-acting beta 2-agonists in asthma—the views of general practitioners and asthma experts in primary and secondary care. *NPJ Prim Care Respir Med*. 2018;28(1):26. doi:10.1038/s41533-018-0096-4
32. Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med*. 2004;140(10):802. doi:10.7326/0003-4819-140-10-200405180-00010
33. Blakeston S, Harper G, Mancebo JZ. Identifying the drivers of patients' reliance on short-acting β2-agonists in asthma. *J Asthma*. 2020;1–8. doi:10.1080/02770903.2020.1761382